UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

August 12, 2013

SUBJECT: **SYNTHETIC PYRETHROIDS:** Summary of Hazard and Science Policy Council (HASPOC) Meeting on July 25, 2013: Recommendations on Data Requirement for Immunotoxicity Studies for Synthetic Pyrethroid Pesticides.

PC Codes: See below
Decision No.: N/A
Petition No.: N/A
Risk Assessment Type: N/A
TXR No.: 0056729
MRID No.: N/A

DP Barcode: N/A
Registration No.: N/A
Regulatory Action: N/A
Case No.: N/A
CAS Nos.: See below
40 CFR: N/A

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THROUGH: Jess Rowland, M.S., Co-Chair
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TO: William Irwin, Ph.D, Toxicologist
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MEETING ATTENDEES

HASPOC Members: Anna Lowit, Elizabeth Mendez, Jeff Dawson, Jess Rowland, Jonathan Chen, Mike Metzger, PV Shah

Presenter: William Irwin

Other Attendees: Anwar Dunbar, Jonathan Leshin, Julie Van Alstine, Linda Taylor, Monique Perron, Ronnie Bever, Uma Habiba, Wade Britton

I. PURPOSE OF MEETING

In accordance with the revised 2007 40 CFR Part 158 Toxicology Data Requirements, an immunotoxicity study is required for food and non-food use pesticides. The HED Hazard and Science Policy Council (HASPOC) met on July 25, 2013 to determine the need for the immunotoxicity study (870.7800) for the following synthetic pyrethroid pesticides.

Chemical	PC Code	CAS Number
Beta Cyfluthrin	118831	68359-37-5
Bifenthrin	128825	82657-04-3
Bioallethrin	004003	584-79-2
Cyfluthrin	128831	68359-37-5
Cyhalothrin	128867	68085-85-8
Deltamethrin	097805	52918-63-5
d-Phenothrin	069005	26002-80-2
Esbiothrin	004007	28434-00-6
Gamma Cyhalothrin	128807	76703-62-3
Lambda Cyhalothrin	128897	91465-08-6
Metofluthrin	109709	240494-70-6
Permethrin	109701	52645-53-1
Prallethrin	128722	23031-36-9
Resmethrin	097801	10453-86-8
S-Bioallethrin (Esbiol)	004004	28434-00-6
Tau-fluvalinate	109302	102851-06-9
Zeta Cypermethrin	209600	52315-07-8

II. SUMMARY OF USE PROFILE, EXPOSURE, AND HAZARD CONSIDERATIONS

a. Use Profile:

Synthetic pyrethroids are a class of synthetic insecticides which are structurally based on the pyrethrins, botanical insecticides extracted from *Chrysanthemum cinerariaefolium.* Pyrethrins are potent insecticides with relatively low mammalian toxicity but are sensitive to air and light. Hence, the use of pyrethrins for crop protection and to control disease-carrying insects is limited. With an altered structure, the pyrethroids are more photostable, while retaining the insecticidal activity of the pyrethrins. Thus, pyrethroids are widely used today in agriculture and in medical and veterinary products. The use profile for the synthetic pyrethroid pesticides is presented in Appendix 1.

b. Toxicity Profiles:

Pyrethroids, the synthetic derivatives of the pyrethrins, have evolved structurally over the past several decades. However, the basic components of pyrethrins, a chrysanthamic acid linked to an aromatic alcohol through an ester linkage have been conserved. Structural modifications such as the addition of halogens to the chrysthanthamic acid and aromatic alcohol moieties and the addition of the α-cyano group have increased photostability, insecticidal potency, and in some incidences, stereoisomerism of the pyrethroids. As a point of reference, pyrethroids lacking the α-cyano group are referred to as Type I and those with the α-cyano group are referred to as Type II pyrethroids. The naturally occurring pyrethrins and synthetic pyrethroids share the same mode of action (MOA; USEPA, 2009): interaction with voltage-gated sodium channels (VGSCs).

High doses of pyrethroids in laboratory animals result in one of two syndromes: 1) the T-syndrome associated with Type I pyrethroids and 2) the CS-syndrome associated with Type II pyrethroids. The neurotoxic behaviors elicited by Type I pyrethroids are aggression, hyperexcitability, fine tremor, prostration with coarse whole body tremor, increased body temperature, coma, and death. These neurobehavioral responses are termed the T-syndrome because of the fine tremors induced by the Type I pyrethroids. For Type II pyrethroids, the neurotoxic behaviors include pawing and burrowing, salivation, hyperexcitability, abnormal hind limb movements, coarse whole body tremor, sinuous writhing, coma, and death. These neurobehavioral responses are termed the CS-syndrome for the choreoathetosis (i.e., whole body writhing) and salivation. Some pyrethroids such as fenpropathrin and esfenvalerate, are considered mixed (Type I/II) because they elicit mixed behaviors of both the T- and CS-syndromes. The T- and CS-syndromes are considered to be acute responses to pyrethroid exposure and are dose-dependent.

In mammals, the onset of neurobehavioral effects occur within a few minutes to over an hour, depending on the route of exposure and chemical, but can take 2-8 hours to peak. Recovery from pyrethroid toxicity is rapid, typically within 24-48 hours. Mammals, unlike insects, have extensive enzyme systems capable of metabolizing and detoxifying the pyrethroids. This difference in physiology makes pyrethroids orders of magnitude less toxic in mammals compared to insects. Pyrethroids delay the inactivation of affected VGSCs, allowing for an increase in sodium ion influx and resulting in delayed repolarization. The delay for cyano-containing (Type II) pyrethroids is about 200 ms and results in a depolarization dependent block of the neuronal action potentials and toxicity. The delay for non-cyano (Type I) pyrethroids is even shorter (about 20 ms) and results in rapid repetitive firing of action potentials and toxicity. As a result, the acute duration is the focus of most pyrethroid risk assessments.

Many studies have shown that behavioral responses, particularly measured in the rat, can be used as sensitive indicators of pyrethroid toxicity (Wolansky and Harrill, 2008). More contemporary studies were designed to detect behavioral changes at a broad range of doses including both lower doses as well as high-doses. Some of these studies include evaluation of motor activity, coordination, neuromuscular response, tremors, acoustic startle response, learning and memory, somatosensory response, social/sexual interactions and behavior to handling, and the functional observation battery (FOB).

Two literature studies (Wolansky *et al*., 2006 and Nemec, 2006) are available that examined the acute neurotoxicity of a variety of pyrethroids. The Wolansky *et al.* (2006) study provides high quality motor activity data while the Nemec (2006) study provides specially designed FOB evaluation focused on pyrethroid toxicity. Neurotoxicity consistent with the pyrethroid MOA is more commonly observed in acute neurotoxicity studies in rats and/or acute and chronic studies in dogs and therefore these studies frequently provide the most sensitive endpoints for this class. Points of Departures (PODs) based on neurotoxic effects have been selected for overall risk assessments for use in single chemical risk assessments

c. <u>Indicators for Potential Immunotoxicity</u>

Parameter	Findings
Hematology Indicators (WBC changes)	There was no evidence of changes in WBC for any of the other chemicals.
Clinical Chemistry Indicators (A/G Ratio)	There was no evidence of alterations in these clinical chemistry indicators for any of the chemicals.
Organ Weight Indicators (Spleen, Thymus)	There was no evidence of changes in absolute or relative weights of spleen and/or thymus for any of the chemicals.
Histopathology Indicators (Spleen, Thymus, Lymph nodes)	There was no evidence of histopathological alterations in the spleen, thymus or lymph nodes for any of the chemicals.

Chemical[1]	Immunotoxicity DER TXR#	Toxicology Findings
Beta Cyfluthrin	--	Target is neuromuscular system; reduction in leukocytes in 28-day inhalation study (NOAEL=0.12, LOAEL=1.6 mg/kg/day) Wolansky BMD_L=1.17 mg/kg, BMD=1.42 mg/kg
Bifenthrin	--	Target organ is the neuromuscular system
Bioallethrin	--	Target organs are liver and neuromuscular system
Cyfluthrin	--	Target is neuromuscular system; reduction in leukocytes in 28-day inhalation study (NOAEL=0.12, LOAEL=1.6 mg/kg/day) Wolansky BMD_L=1.17 mg/kg, BMD=1.42 mg/kg
Cyhalothrin	--	Target organ is the neuromuscular system
Deltamethrin	--	Target organ is the neuromuscular system
d-Phenothrin	--	Targets organs are the liver, adrenal gland, neuromuscular system, kidney, heart; increased spleen weight in reproduction study (NOAEL=50, LOAEL=150 mg/kg/day); dilation of lymph nodes in chronic rat study (NOAEL=50, LOAEL=150 mg/kg/day); increased A/G ratio in rat carcinogenicity study (NOAEL=51, LOAEL=553 mg/kg/day); In reference chronic dog study NOAEL=7.1 (LOAEL=26.8 mg/kg/day based on hepatocellular degeneration, adrenal cortex focal degeneration)
Esbiothrin	--	Target organs are liver and neuromuscular system
Gamma Cyhalothrin	--	Target organ is neuromuscular system
Lambda Cyhalothrin	--	Target organ is neuromuscular system
Metofluthrin	--	Target organs are liver and neuromuscular system
Permethrin	--	Target organ is neuromuscular system
Prallethrin	--	Target organ is neuromuscular system
Resmethrin	--	Target organs are liver and neuromuscular system; thymic lymphocytolysis and decreased spleen weight in a 4 week oral study at 994.5 mg/kg/day (NOAEL=452.3 mg/kg/day, MRID 43338601); elevated A/G ratio in 90-day inhalation study at 1.0 mg/L (NOAEL~54, LOAEL~180 mg/kg/day) Wolansky BMD_L=75.89 mg/kg, BMD=162.32 mg/kg
S-Bioallethrin (Esbiol)	--	Target organs are liver and neuromuscular system
Tau-fluvalinate	--	Target organs are liver, kidney and neuromuscular system; enlarged lymph nodes in a 90-day rat study (NOAEL=3, LOAEL=30 mg/kg/day) ACN Study NOAEL=0.5 mg/kg, LOAEL=1.0 mg/kg
Zeta Cypermethrin	--	Target organ is the neuromuscular system; decreased WBC in 90-day oral study (NOAEL=13.8, LOAEL=28.2 mg/kg/day) Wolansky BMD_L=7.16 mg/kg, BMD=11.19 mg/kg

d. Evidence for Immunotoxicity from SAR Chemicals – Retrospective Analysis.

Acceptable guideline immunotoxicity studies have been submitted for 7 synthetic pyrethroid pesticide chemicals. No immunotoxicity was observed at the highest dose tested for all 7 chemicals, with etofenprox tested in both rats and mice.

Alpha Cypermethrin/Cypermethrin	
MRID No.	48273201 and 48540601
Immunotoxicity NOAEL	34 mg/kg/day (HDT)
Immunotoxicity LOAEL	Not Established
Basis for LOAEL	None
Systemic toxicity NOAEL	34 mg/kg/day
Systemic Toxicity LOAEL	Not Established
Basis for the LOAEL	None

Esfenvalerate	
MRID No.	48413001
Immunotoxicity NOAEL	13.07 mg/kg/day (M) and 14.59 mg/kg/day (F) (HDT)
Immunotoxicity LOAEL	Not Established
Basis for LOAEL	None
Systemic toxicity NOAEL	4.49 mg/kg/day (M) and 4.89 mg/kg/day (F)
Systemic Toxicity LOAEL	13.07 mg/kg/day (M) and 14.59 mg/kg/day (F)
Basis for the LOAEL	Clinical signs of neurotoxicity (ataxia, tremors, piloerection, hypersensitivity, splayed limbs, and decreased muscle tone) in both sexes, and decreased thymus weights in females.

Fenpropathrin	
MRID No	48536804
Immunotoxicity NOAEL	42 mg/kg/day (HDT)
Immunotoxicity LOAEL	Not Established
Basis for LOAEL	None
Systemic toxicity NOAEL	26 mg/kg/day
Systemic Toxicity LOAEL	42 mg/kg/day
Basis for the LOAEL	Decreases in body weight and body weight gain

Flumethrin	
MRID No.	48240250
Immunotoxicity NOAEL	11.7mg/kg/day (M) and 12.3 mg/kg/day (F) (HDT)
Immunotoxicity LOAEL	Not Established
Basis for LOAEL	None
Systemic toxicity NOAEL	3 mg/kg/day (M) and 3.5 mg/kg/day (F)
Systemic Toxicity LOAEL	11.7mg/kg/day (M) and 12.3 mg/kg/day (F)
Basis for the LOAEL	Decreased body weight

Tefluthrin	
MRID No.	48756301
Immunotoxicity NOAEL	62 mg/kg/day (HDT)
Immunotoxicity LOAEL	Not Established
Basis for LOAEL	None
Systemic toxicity NOAEL	31 mg/kg/day

Systemic Toxicity LOAEL	62 mg/kg/day
Basis for the LOAEL	Decreased body weight gain

Tetramethrin	
MRID No.	48540401
Immunotoxicity NOAEL	545 mg/kg/day (HDT)
Immunotoxicity LOAEL	Not Established
Basis for LOAEL	None
Systemic toxicity NOAEL	102 mg/kg/day
Systemic Toxicity LOAEL	257 mg/kg/day
Basis for the LOAEL	Decreased body weight gain

III. STUDY WAIVER REQUESTS

A waiver is recommended for an immunotoxicity study for the synthetic pyrethroid pesticides based on the following considerations:

- There was no consistent evidence of adverse effects on the immune system in mice, rats, or dogs in the database for any of the pyrethroid pesticides.
- The nervous system is the target organ for this chemical class, and neurotoxicity characterized as clinical signs, behavioral, neuropathology, or body weight changes are the primary toxicological endpoints of concern and were used in risk assessments.
- Synthetic pyrethroids do not belong to a class of chemicals (e.g., the organotins, heavy metals, or halogenated aromatic hydrocarbons) that would be expected to be immunotoxic. There was no evidence of immunotoxicity with seven other structurally-related synthetic pyrethroids, namely, alpha cypermethrin, cypermethrin, esfenvalerate, etofenprox, fenpropathrin, flumethrin, tefluthrin, and tetramethrin.
- PODs based on the most sensitive endpoints obtained via the appropriate routes of exposure in the most sensitive species are currently used for dietary and non-dietary risk assessments. The Wolansky acute oral study was utilized to determine the PODs for multiple pyrethroids.

All these factors indicate that an immunotoxicity study would most likely not provide a more sensitive endpoint or a POD for than currently being used for human health risk assessment..

IV. HASPOC CONCLUSIONS

The HASPOC, based on a weight of evidence approach, concludes that immunotoxicity studies are not required as this time for beta cyfluthrin, bifenthrin, bioallethrin, cyfluthrin, cyhalothrin, deltamethrin, d-phenothrin, esbiothrin, fenvalerate, gamma cyhalothrin, lambda cyhalothrin, metofluthrin, permethrin, prallethrin, resmethrin, s-bioallethrin (esbiol), tau-fluvalinate, and zeta-cypermethrin. An immunotoxicity study is not anticipated to provide a lower POD or result in a more sensitive endpoint than those already used.

Appendix 1: Use Profiles of Synthetic Pyrethroid Pesticides

Allethrin: The allethrin series of pyrethroid insecticides include **bioallethrin (**004003), **esbiol** (004004), **esbiothrin** (004007), and **pynamin forte** (004005). The allethrins all have the same chemical structure but have several isomers which are "mirror images" of each other. The allethrins differ only in the percentage of isomers present in each pesticide. Allethrins are used as space sprays in a wide variety of indoor areas such as greenhouses, commercial institutions, and residences. There are no food uses for the allethrins; a Federal Register final rule revoking all food tolerances was published on September 29, 2004. There is a pending petition for the establishment of a permanent food handling establishment tolerance set at 1.0 ppm. A food handling establishment is any place other than a residential kitchen in which food is held, processed, prepared, and/or served.

Bifenthrin: Bifenthrin is a pyrethroid insecticide/miticide used to control termites and insects in both agricultural and residential settings. Bifenthrin is currently registered as emulsifiable concentrate (EC), wettable-powder (WP), granular (G), and flowable-concentrate (FlC) formulations. Bifenthrin is registered for use by occupational handlers on a variety of agricultural commodities, and by occupational and residential handlers on turf and indoor environments (crack and crevice). Exposure to bifenthrin is expected to be short- and intermediate-term durations for occupational handlers and short-term for residential handlers and following use in residential settings. Bifenthrin may be applied with handheld, ground, and aerial equipment

Cyfluthrin/beta-Cyfluthrin: Cyfluthrin and beta-cyfluthrin are pyrethroid insecticides registered to Bayer CropScience for control of various insect pests on a wide variety of crops. Both compounds are mixtures of four diastereomers, Isomers I to IV, with beta-cyfluthrin being enriched in Isomers II and IV. Permanent tolerances are established for residues of cyfluthrin (40 CFR §180.436) in or on a wide variety of plant commodities, at levels ranging from 0.01 ppm in peanuts, tree nuts, and tuberous and corm vegetables, to 150 ppm in aspirated grain fractions (AGF). Tolerances are also currently established in animal commodities, at levels ranging from 0.01 ppm in eggs and poultry fat, meat, and meat byproducts, to 5.0 ppm in milk fat. The Agency has previously concluded that tolerances for cyfluthrin will also cover beta-cyfluthrin, provided that the use rates of beta-cyfluthrin are no more than half the use rates of cyfluthrin (based on isomer enrichment ratios).

Cypermethrin: a molecule with three asymmetric carbon atoms, is a combination of 8 stereoisomers with percentage compositions ranging from 11-14%. Cypermethrin is registered for foliar applications to control a wide range of pests, particularly lepidoptera, on food/feed crops including leafy *Brassica* greens and head and stem *Brassica* crop subgroups, cotton, garlic, lettuce (head), onions (dry bulb and green), pecans, and shallots using ground, sprinkler irrigation, or aerial equipment. Cypermethrin is additionally registered as a soil residual termiticide, for outdoor pest control to structures and lawns, indoor pest control (dilutable formulations for crack and crevice or spot treatments, total release foggers or aerial space sprays), livestock ear tags, and for application to horses. It can be used in industrial, commercial, and residential sites. Single active ingredient formulations of cypermethrin are available as EC, soluble concentrate/liquid (SC/L), G, and WP. Cypermethrin is compatible with a number of insecticides and fungicides. Tolerances for cypermethrin are listed under 40 CFR§180.418(a)(1).

Delatamethrin: Deltamethrin is a broad-spectrum pyrethroid insecticide that is registered in the U.S. for direct application to a wide variety of food/feed crops, for use on stored grains, for use in food/feed handling establishments, and for a variety of residential uses. Two EC formulations of deltamethrin are currently registered to Bayer CropScience for use on food and feed crops. One is a 1.5 pound active ingredient per gallon (lb ai/gal) EC (Decis 1.5EC Insecticide, EPA Registration #264-1011), and the other is a 0.2 lb ai/gal EC (Decis 0.2EC Insecticide, EPA Registration #264-1007). Tolerances are established under 40 CFR §180.435 for residues of deltamethrin that result from agricultural uses as well as food and feed handling establishment uses.

d-Phenothrin: Phenothrin is not currently registered for direct application to agricultural crops and there are currently no tolerances for specific raw agricultural commodities. Phenothrin is used to control adult mosquitoes in residential and outdoor recreational areas. It is also used as an insecticide and miticide in commercial, industrial, and institutional non-food areas, in transport vehicles such as aircraft, ships, railroad cars and truck trailers, in homes and gardens, in greenhouses, in pet quarters, and on pets. Phenothrin is applied as a mosquitocide either by aircraft or truck-mounted ultra-low volume (ULV) sprayers. Based on information provided by HED's Biological and Economical Analysis Division (BEAD) approximately 420 pounds of phenothrin were used in California in 2004, which represents a significant increase over the estimated 210 pounds used in California in 2003. According to BEAD, usage information was not available for any other states (J. Carter, D326954, 6/31/06). Phenothrin is available primarily as ready-to-use, pressurized liquid and emulsifiable concentrate formulations. It is applied by commercial and residential applicators using a variety of application methods and equipment.

The registrant, McLaughlin Gormley King (MGK) Company, has initiated a Section 3 request to expand the mosquitocide use of phenothrin to permit application over agricultural lands and has petitioned the Agency to establish a tolerance of 0.01 ppm for residues of D-Phenothrin on all food/feed crops after wide-area mosquito adulticide application.

Gama Cyhalothrin: Gamma-cyhalothrin is a single, resolved isomer of the pyrethroid insecticide cyhalothrin. Uses of the insecticide include in food-handling establishments, on okra and pistachios, and use in ear tags for beef and non-lactating dairy cattle.

Lambda Cyhaltorhin: Lambda-cyhalothrin is a synthetic pyrethroid insecticide used to control a wide range of pests on food/feed crops and livestock, as well as in and around buildings and structures. Lambda-cyhalothrin is an enriched isomer of cyhalothrin. It is currently used on a wide range of pests (including aphids, adult Japanese beetles, grasshoppers, and butterfly larvae) in a variety of applications. It may also be used for structural pest management (termiticide), and in public health applications to control insects (such as mosquitoes, cockroaches, ticks, and flies) which may act as disease vectors. Another use is as a pour-on insecticide, which is applied down the backline of beef cattle for control of lice and horn flies. There are existing residential uses for lambda-cyhalothrin.

Methofluthrin: Metofluthrin's currently registered repellent products including impregnated paper repellent strips, a personal outdoor insect repellent fan, and a recently registered candle product. There are no food/feed uses and no drinking water exposure is expected from the repellent uses.

Permethrin: Permethrin is a broad-spectrum pyrethroid insecticide that is registered in the U.S. for use in a wide variety of residential settings, on a wide variety of crops, and also as a pediculicide for the treatment of head lice and scabies. Based on the current use profile, exposures can be expected to occur via the dietary (food and drinking water), residential (handler and post-application), and occupational (handler and post-application) routes for permethrin.

Prallethrin: Prallethrin is a pyrethroid insecticide that is currently registered for the control of a variety of indoor and outdoor pests found in homes and commercial settings, including food handling establishments. It is also registered for the control of a number of veterinary and public health pests. In 40 CFR §180.545, a tolerance of 1.0 ppm is established for residues of prallethrin resulting from use in food handling establishments. The tolerance is established in terms of (*RS*)-2-methyl-4-oxo-3-(2-propynyl)cyclopent-2-enyl(*IR*)-cis,trans-chrysanthemate.

Registered formulations include pressurized sprays (aerosols) and liquids. They are packaged for application as space and surface sprays and as total release foggers. There are also spray, wipe, and shampoo formulations for use on dogs and horses. Because of the broad-spectrum insecticidal properties of prallethrin, many end-use products are labeled for use in multiple sites. To broaden the efficacy of prallethrin, the registrants have formulated it with a number of other insect control agents such as insecticide synergists (piperonyl butoxide and MGK 264) and other pyrethroids (sumithrin, esfenvalerate, etc.).

Resmethrin: Resmethrin, ([5-(phenylmethyl)-3-furanyl] methyl 2,2-dimethyl-3-(2-methyl-1-propenyl)-clcloproanecarboxylate) is a Type I pyrethroid insecticide. Resmethrin is used for broad spectrum control of insects on ornamental plants, pets and their dwellings, and in outdoor and indoor areas of residential, commercial, and industrial sites

Tau-fluvalinate: Tau-fluvalinate, a type II class pyrethroid, is registered as a post-emergent insecticide/miticide for the control of a variety of insects in beehives and various outdoor or greenhouse settings.

Zeta Cypermethrin: is an enriched enantiomer of cypermethrin consisting of the 4 stereoisomers with an “S” configuration at the cyano bearing carbon at 24% each, and 4 insecticidally less active stereoisomers at a concentration of 1% each. Zeta-cypermethrin has been registered on the same agricultural crops as cypermethrin plus many more. When applied on agricultural crops, the typical use rate for zeta-cypermethrin is one-half that for cypermethrin because the concentration of the most insecticidally active isomers are about two times higher in zeta-cypermethrin than in cypermethrin. Tolerances for zeta-cypermethrin are listed under 40 CFR §180.418(a)(2).